



Clinical paper

Low cerebral blood flow after cardiac arrest is not associated with anaerobic cerebral metabolism[☆]Cornelia W. Hoedemaekers^{a,*}, Philip N. Ainslie^b, Stijn Hinssen^c, Marcel J. Aries^d, Laurens L. Bisschops^a, Jeannette Hofmeijer^c, Johannes G. van der Hoeven^a^a Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, The Netherlands^b Centre for Heart, Lung and Vascular Health, University of British Columbia, British Columbia, Canada^c Department of Neurology, Rijnstate Hospital, Arnhem and department of Clinical Neurophysiology, University of Twente, Enschede, The Netherlands^d Department of Intensive Care, University of Maastricht, Maastricht University Medical Center, Maastricht, The Netherlands

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ABSTRACT

Aim of the study: Estimation of cerebral anaerobic metabolism in survivors and non-survivors after cardiac arrest.**Methods:** We performed an observational study in twenty comatose patients after cardiac arrest and 19 healthy control subjects. We measured mean flow velocity in the middle cerebral artery (MFV_{MCA}) by transcranial Doppler. Arterial and jugular blood samples were used for calculation of the jugular venous-to-arterial CO₂/arterial to-jugular venous O₂ content difference ratio.**Results:** After cardiac arrest, MFV_{MCA} increased from 26.0[18.6–40.4] cm/sec on admission to 63.9[48.3–73.1] cm/sec after 72 h ($p < 0.0001$), with no significant differences between survivors and non-survivors ($p = 0.4853$). The MFV_{MCA} in controls was 59.1[52.8–69.0] cm/sec. The oxygen extraction fraction (O₂EF) was 38.9[24.4–47.7]% on admission and decreased significantly to 17.3[12.1–26.2]% at 72 h ($p < 0.0001$). The decrease in O₂EF was more pronounced in non-survivors ($p = 0.0173$). O₂EF in the control group was 35.4[32.4–38.7]%. The jugular bulb-arterial CO₂ to arterial-jugular bulb O₂ content difference ratio was >1 at all time points after cardiac arrest and did not change during admission, with no differences between survivors and non-survivors. Values in cardiac arrest patients were similar to those in normal subjects.**Conclusions:** In this study, low CBF after cardiac arrest is not associated with anaerobic metabolism. Hypoperfusion appears to be the consequence of a decrease of neuronal functioning and metabolic needs. Alternatively, hypoperfusion may decrease cerebral metabolism. Subsequently, metabolism increases in survivors, consistent with resumption of neuronal activity, whereas in non-survivors lasting low metabolism reflects irreversible neuronal damage.© 2017 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Introduction

Cardiac arrest is a leading cause of death in western countries, and most patients die from neurological injury [1]. Abnormal cerebral blood flow (CBF) is a key feature of post-anoxic brain injury. In comatose patients after cardiac arrest, CBF is initially low and gradually restores towards normal values during the first 72 h after return of spontaneous circulation (ROSC) [2–4]. This hypoperfu-

sion after cardiac arrest can potentially cause a mismatch between cerebral oxygen demand and supply. Previous studies reported a decrease in the cerebral metabolic rate of oxygen, secondary to the cardiac arrest, providing a teleological mechanism to match this decreased supply of oxygen and nutrients to the brain [2–4]. It is yet unknown, whether this decrease in metabolic rate is proportional to the decrease in CBF: disproportional adaptation of CBF to metabolism may result in hypoperfusion and ischemia or hyperperfusion and hyperemia.

Recently, the mixed venous-arterial CO₂ (C_{v-a}CO₂) to arterial-venous O₂ (C_{a-v}O₂) content difference ratio (C_{v-a}CO₂/C_{a-v}O₂), has been suggested as a surrogate marker for the balance between oxygen consumption (VO₂) and CO₂ production (VCO₂) in sepsis patients. Under normal aerobic

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conditions, O_2 delivery matches CO_2 production, and the $C_{a-v}O_2$ approximates the $C_{v-a}CO_2$. Although hypoperfusion decreases both O_2 consumption and aerobic CO_2 production, anaerobic glycolysis and ATP hydrolysis increase anaerobic CO_2 production, leading to an increased $C_{v-a}CO_2$ relative to $C_{a-v}O_2$ [reviewed in [5]].

Oxygen-derived or CO_2 -derived parameters as a single parameter correlate poorly with anaerobic metabolism. The $C_{a-v}O_2$ cannot discriminate between true tissue hypoxia and states of a reduced demand without hypoxia. Anaerobic CO_2 production will result in an increased $C_{v-a}CO_2$ [6]. At the same time, due to the so-called CO_2 stagnation phenomenon, slow microcirculatory blood flow will result in increased transfer of CO_2 from the tissue to the microcirculation, resulting in an increased $C_{v-a}CO_2$ in the absence of tissue hypoxia. In sepsis, the $C_{v-a}CO_2/C_{a-v}O_2$ ratio is strong marker for the detection of anaerobic metabolism and more reliable than conventional parameters such as hyperlactatemia or mixed venous oxygen saturation [6–8]. An increased $C_{v-a}CO_2/C_{a-v}O_2$ ratio was associated with a poor outcome and severity of organ dysfunction in sepsis patients [9].

CBF is low after cardiac arrest and may potentially result in increased anaerobic metabolism, despite normal jugular bulb lactate concentrations and normal jugular bulb oxygen saturation. The aim of the present study was to further elucidate the coupling between cerebral oxygen delivery and demand during the post-cardiac arrest syndrome by determination of parameters of cerebral anaerobic metabolism. We hypothesized that the changes in CBF after cardiac arrest were related to changes in metabolism. In analogy to the $C_{v-a}CO_2/C_{a-v}O_2$ ratio, we calculated the jugular venous-to-arterial CO_2 /arterial to-jugular venous O_2 content difference ratio ($C_{j-b}CO_2/C_{a-jb}O_2$) as a measure of anaerobic CO_2 generation in survivors and non-survivors after cardiac arrest. For the first time, in order to obtain normative values, these metrics were also calculated in healthy control subjects.

Material and methods

Study population

We performed a secondary analysis of prospectively collected data from two difference observational studies in 20 comatose patients after out-of-hospital cardiac arrest and 19 healthy controls. The local institutional review boards approved the original studies.

Data from the cardiac arrest patients were prospectively collected from two observational studies that studied the effect of viscosity ($n = 10$ patients) and prolonged hypothermia ($n = 10$ patients) on CBF after cardiac arrest [10,11]. Main inclusion criteria for both studies were Glasgow Coma Scale ≤ 6 after ROSC and age > 18 years. Exclusion criteria included pregnancy, thrombolytic therapy, contraindication for therapeutic hypothermia, and chronic renal or hepatic failure.

Data of 19 normal healthy controls were derived from 2 observational studies on the effects of manipulation of PaO_2 and $PaCO_2$ on the CBF and metabolism [12,13]. The volunteers were non-smokers, had no history of cardiovascular diseases, and were not taking any medications. Only data obtained at sea level were used for this study.

Post-cardiac arrest management

Cardiac arrest patients were admitted to the ICU and treated with mild hypothermia at $33^\circ C$ for 24 or 72 h, followed by passive rewarming. Patients were sedated with propofol and/or midazolam and sufentanil. In case of shivering, patients were paralyzed using intravenous bolus injections of rocuronium.

All patients were intubated and mechanically ventilated, aiming at a $PaO_2 > 75$ mmHg and a $PaCO_2$ between 34 and 41 mmHg. Alpha-stat was used for pH maintenance. Monitoring of blood pressure and arterial blood sampling was performed with the use of a catheter in the radial or femoral artery. Mean arterial pressure (MAP) was maintained between 80 and 100 mmHg with a diuresis of > 0.5 mL/kg/hr. Patients were treated with volume infusion and dobutamine or norepinephrine, if necessary. Blood from the jugular bulb was sampled from a 7-Fr single-lumen jugular bulb catheter.

Data collection

Post-cardiac arrest patients

Demographic and clinical data were collected. Hemodynamic variables, temperature, and SaO_2 were measured continuously.

Transcranial Doppler (TCD) of the middle cerebral artery (MCA) was performed through the temporal window with a 2 MHz probe (Sonosite M-Turbo, Sonoview Nederland BV, Rijswijk, The Netherlands) on admission and at 12, 24, 48 and 72 h thereafter.

Arterial and jugular blood samples were collected for blood gas analysis, lactate and hemoglobin measurements upon admission and at 12, 24, 48 and 72 h. Outcome after cardiac arrest was assessed upon ICU discharge.

Data collection healthy volunteers

The left MCA blood velocity was measured by TCD (Spencer Technologies, Seattle, WA, USA) using a 2-MHz pulsed probe. A 20G arterial catheter (Arrow, Markham, Ontario, Canada) was inserted into the left radial artery, and a jugular bulb catheter (Edwards PediaSat Oximetry catheter, Irvine, CA, USA) was placed into the jugular bulb.

Data analysis

Metabolic parameters were calculated as follows:

Content of arterial (CaO_2) and venous (CvO_2) oxygen were calculated using the equations:

$$CaO_2 \text{ (ml.dl}^{-1}\text{)} = [Hb] \cdot 1.36 \cdot \frac{SaO_2 (\%)}{100} + 0.003 \cdot PaO_2$$

$$CvO_2 \text{ (ml.dl}^{-1}\text{)} = [Hb] \cdot 1.36 \cdot \frac{SvO_2 (\%)}{100} + 0.003 \cdot PvO_2$$

Where 1.36 is the affinity for oxygen to hemoglobin for a given arterial saturation, and 0.003 is the percentage of oxygen dissolved in the blood.

Oxygen extraction fraction (O_2EF) was calculated by:

$$O_2EF (\%) = \frac{CaO_2 - CvO_2}{CaO_2} \cdot 100\%$$

Where arterial and jugular venous O_2 content differences are equal to CaO_2 and CvO_2 , respectively.

The content of carbondioxide in the arterial and jugular bulb venous blood samples was calculated according to Douglas et al [14].

$$CCO_2 \text{ (ml dl}^{-1}\text{)} = \text{plasma } CCO_2 \times \left(1 - \frac{0,0289 \times Hb}{(3,352 - 0,456 \times SO_2) \times (8,142 - pH)} \right),$$

with plasma $CCO_2 = 2,226 \times S \times PCO_2 \times (1 + 10^{pH-pK'})$.

S and pK' are the plasma CO_2 solubility and apparent pK , respectively. These measures are dependent on the temperature (T) and

Table 1
Demographic data post-cardiac arrest patients.

Characteristics	
Men, n (%)	17 (85%)
Age (yr)	66[59.5–73]
BMI (kg/m ²)	26[24.8–26.5]
Primary rhythm, n (%)	
Shockable	10 (50%)
Non-shockable	10 (50%)
Time collapse-ROSC	30 [25–54]
SAPS2	65.5[50.5–71.8]
APACHE II	26[18.8–29.5]
pH upon hospital admission	7.19[7.07–7.27]
BE upon hospital admission (mmol/l)	–9.15[–15.8 to –5.6]
Lactate upon hospital admission (mmol/l)	6.8[3.6–10.9]
Patients died, n (%)	9 (45%)

Data are expressed as median [interquartile range] or as absolute numbers (percentage).

BMI: Body mass index.

ROSC: return of spontaneous circulation.

SAPS2: Simplified Acute Physiology Score.

APACHE II: Acute Physiology and Chronic Health Evaluation II.

calculated as:

$$S = 0,0307 + 0,00057 \times (37 - T) + 0,00002 \times (37 - T)^2 \text{ and} \\ 6,086 + 0,042 \times (7,4 - pH) + (38 - T) \times (0,00472 \\ + 0,00139 \times (7,4 - pH))$$

The jugular bulb-arterial CO₂ content difference was calculated as:

$$C_{jb-a}CO_2(\text{ml dl}^{-1}) = C_{jb}CO_2 - C_aCO_2.$$

The jugular bulb-arterial CO₂ to arterial-jugular bulb O₂ content difference ratio was defined as

$$C_{jb-a}CO_2/C_{a-jb}O_2.$$

Lactate extraction fraction (LacEF) was calculated by:

$$\text{LacEF}(\%) = \frac{\text{Lac}_a - \text{Lac}_v}{\text{Lac}_a} \cdot 100\%$$

Where Lac_a and Lac_v equal the arterial and jugular venous concentration of lactate, respectively.

Statistics

Statistical analysis was performed using GraphPad Prism version 5.0 (GraphPad Software, La Jolla, CA). Normal distribution of the data was verified using the Kolmogorov-Smirnov test. Data in the text are presented as median with 25th and 75th percentile. Changes over time were analyzed with the repeated-measures test (one way ANOVA). Differences between survivors and non-survivors in time were analyzed with two-way analysis of variance.

The Student's *t*-test or the Wilcoxon signed-rank test was used for the comparison between groups, depending on the distribution of the data. A *p*-value of <0.05 was considered to indicate significance.

Results

Demographic and clinical data

We included 20 patients after cardiac arrest. Demographic and clinical data are summarized in Table 1. Nine patients died in the ICU: 5 patients because of severe post-anoxic brain damage, 3

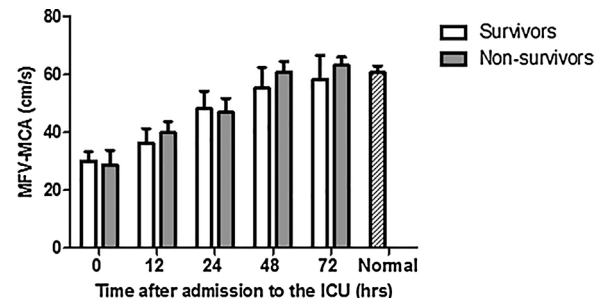


Fig. 1. Mean flow velocity in the middle cerebral artery in survivors (white bars) and non-survivors (grey bars) during the first 72 h after cardiac arrest. Striped bar represents values in normal control subjects. Data are expressed as mean ± SD.

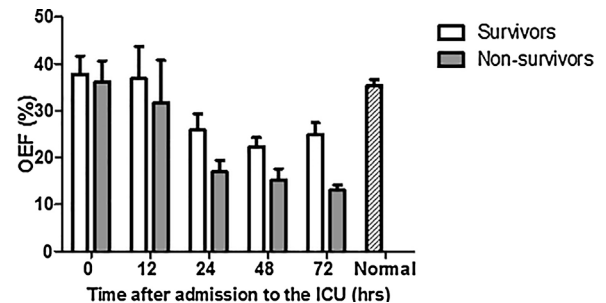


Fig. 2. Oxygen extraction fraction in survivors (white bars) and non-survivors (grey bars) during the first 72 h after cardiac arrest. Striped bar represents values in normal control subjects. Data are expressed as mean ± SD.

patients because of circulatory failure and in 1 patient active treatment was withdrawn because of severe preexisting pulmonary disease. PaO₂ and PaCO₂ were stable during admission with no significant changes between survivors and non-survivors (data not shown). Hemoglobin concentration decreased significantly from 13.4[11.8–15.2] g/dL upon admission to 11.3[9.4–11.8] g/dL at 72 h (*p* < 0.0001), with no statistically significant differences between survivors and non-survivors (*p* = 0.54). Use of doses of sedatives, inotropes and vasopressors did not differ between survivors and non-survivors.

19 subjects (17 males, 2 females) were included in the control group, with a median age of 26[23.5–31] yrs. Values of PaO₂ and PaCO₂ were essentially equal to those in cardiac arrest patients (data not shown). The hemoglobin concentration in the control group was 14.8[14.0–15.1] g/dL.

Cerebral blood flow

In the post-cardiac arrest group, the MFV_{MCA} increased from 26.0[18.6–40.4] cm/sec on admission to 63.9[48.3–73.1] cm/sec after 72 h (*p* < 0.0001), with no significant differences between survivors and non-survivors (*p* = 0.49) (Fig. 1). The MFV_{MCA} in healthy controls was 59.1[52.8–69.0] cm/sec.

Metabolic variables

The O₂EF was 38.9[24.4–47.7]% on admission and decreased significantly to 17.3[12.1–26.2] % at 72 h (*p* < 0.0001). The decrease in O₂EF was significantly more pronounced in non-survivors (*p* = 0.02) (Fig. 2). The O₂EF in the control group was 35.4[32.4–38.7] %.

The C_{jb-a}CO₂ decreased from 7.68[4.04–12.1] upon admission to 3.32[1.56–4.70] ml/dl at 72 h (*p* = 0.08). The decrease in jugular bulb-arterial CO₂ content difference was significantly stronger in non-survivors compared to survivors (*p* = 0.0061) (Fig. 3). The C_{jb-a}CO₂ in the control group was 7.88[6.96–9.09] ml/dl and equal

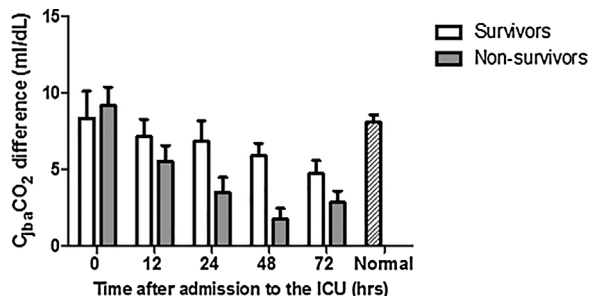


Fig. 3. The jugular bulb-arterial CO₂ content difference in survivors (white bars) and non-survivors (grey bars) during the first 72 h after cardiac arrest. Striped bar represents values in normal control subjects. Data are expressed as mean ± SD.

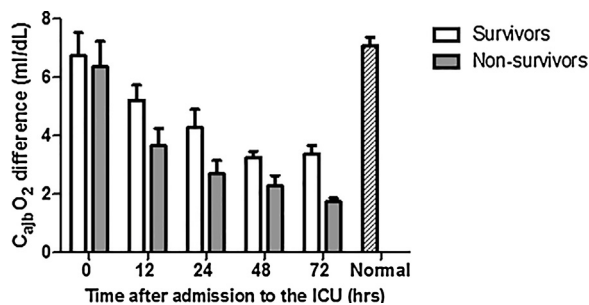


Fig. 4. The arterial-jugular bulb O₂ content difference in survivors (white bars) and non-survivors (grey bars) during the first 72 h after cardiac arrest. Striped bar represents values in normal control subjects. Data are expressed as mean ± SD.

to values of cardiac arrest patients upon admission to the ICU. The decrease in $C_{jb-a}CO_2$ was predominantly caused by a decrease in jugular bulb CO₂ content (Table 2, Supplementary digital content).

The $C_{a-jb}O_2$ decreased from 6.0[4.08–8.43] ml/dl at admission to 1.85[1.48–3.63] ml/dl at 72 h ($p < 0.0001$). The $C_{a-jb}O_2$ was lower in patients after 72 h compared to healthy controls (normal values 7.18[6.33–7.97] ml/dl, $p < 0.0001$). The $C_{a-jb}O_2$ decreased significantly in the first 3 days after admission, with a larger decrease in non-survivors compared to survivors ($p < 0.0001$), (Fig. 4). This decrease in $C_{a-jb}O_2$ was mainly explained by a decrease in arterial oxygen content during the admission (Table 2, Supplementary digital content).

The $C_{jb-a}CO_2/C_{a-jb}O_2$ was >1 at all time points in patients after cardiac arrest and did not change significantly during admission: 1.28[0.98–1.46] at admission and 1.27[0.77–1.79] at 72 h, with no differences between survivors and non-survivors (Fig. 5). In the healthy control group the ratio was 1.16[1.01–1.25].

Arterial and jugular bulb lactate concentrations decreased significantly in the first 3 days after admission from 3.15[1.95–5.93] to 1.65[1.40–2.18] mmol/l and from 3.55[2.05–5.78] to 1.70[1.50–2.48] mmol/l, respectively ($p < 0.0001$). Survivors after cardiac arrest had lower arterial and jugular bulb lactate concentrations than non-survivors (data not shown). Arterial and jugular bulb lactate concentrations of control subjects were significantly lower at all time points (0.8[0.6–1.05] and 0.9[0.6–1.05] mmol/l respectively, $p < 0.0001$) (data not shown). The lactate EF was 4.35[0.0–13.8]% upon admission and 0.0[–10.5–10.5]% at 72 h ($p = 0.40$). There was no significant difference between survivors and non-survivors ($p = 0.48$) (data not shown).

The metabolic variables were not different between the group treated with 24 or 72 h of hypothermia (Table electronic supplement).

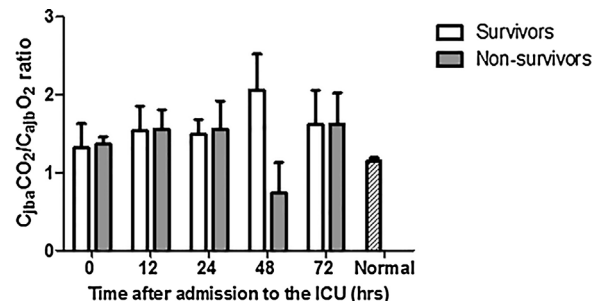


Fig. 5. The jugular bulb-arterial CO₂ to arterial-jugular bulb O₂ content difference ratio in survivors (white bars) and non-survivors (grey bars) during the first 72 h after cardiac arrest. Striped bar represents values in normal control subjects. Data are expressed as mean ± SD.

Discussion

In the first hours after cardiac arrest, MVF_{mca} was low, while O₂EF remained within in the normal range. Despite this apparent mismatch, we found no evidence of tissue hypoxia, indicating a well-adjusted balance between oxygen delivery and consumption in both survivors and non-survivors. These data strongly indicate that cerebral metabolism is decreased, especially in the first hours after the arrest. Reductions in aerobic metabolism and O₂EF were more apparent in non-survivors after cardiac arrest, and likely reflective of irreversible neuronal damage.

The $C_{jb-a}CO_2$ decreased during admission, due to an absolute decrease in venous jugular bulb CO₂ content. This decreased $C_{jb-a}CO_2$ is most consistent with a decrease in cerebral glycolysis and CO₂ production after ROSC, suggesting a decreased metabolism. This decrease was strongest in non-survivors, suggesting less CO₂ production in irreversibly damaged brain tissue. The jugular bulb CO₂ content gradually restored towards normal values in patients with a good outcome, indicating a restoration of metabolism in these cells. The changes in jugular CO₂ content were accompanied by a continuing decrease in O₂EF in patients with a poor outcome, whereas a gradual restoration of O₂EF towards normal values occurred in surviving patients. Taken together, these metabolic changes after cardiac arrest are best explained by restoration of neuronal functioning in patients that eventually recover, and irreversible loss of functional cerebral tissue in non-survivors.

A decrease in cerebral metabolism is in agreement with previous studies in humans and animal models [15–20]. On the one hand, the low CBF state in the first hours after cardiac arrest renders the brain at risk for ischemia. Alternatively, the hypoperfusion follows the inactivity of the brain. Low energy supply leads to an abrupt discontinuation of various neuronal functions, mainly synaptic neurotransmission [21]. This reduction in neurotransmission lowers metabolism quickly, and is widely assumed to be a compensatory mechanism [22]. In turn, this leads to a reduction of metabolism and a consequent reduction of perfusion. This hypothesis is in agreement with our repeated observations with continuous EEG: cardiac arrest leads to iso-electric patterns within 10–40 s in all patients, reflecting an abrupt stopping of cortical synaptic transmission. In recovering patients, rhythms restore within 12–24 h. Otherwise, patterns remain disturbed in patients that insufficiently recover neurologically [23].

The venous-arterial CO₂ to arterial-venous O₂ content difference ratio as a parameter for anaerobic metabolism was not significantly different between patients after cardiac arrest and the control group, and independent of outcome. These data suggest

that cerebral metabolism after cardiac arrest is mainly aerobic in nature, even in patients with a poor neurologic outcome.

To date, most studies on cerebral ischemia-reperfusion injury after cardiac arrest have focused on oxygen-derived parameters to determine the balance between oxygen supply and demand. By calculation of a more specific parameter, we demonstrated that cerebral metabolism after cardiac arrest is mainly aerobic in nature, even in patients with a poor outcome. As supply of oxygen was not a limiting factor in this study, it seems unlikely that enhancement of CBF in these patients will improve the post-anoxic encephalopathy. Treatment with hypothermia at 33 °C does not confer benefit compared to treatment at 36 °C, neither does prolonged hypothermia for 48 h compared to 24 h improve outcome after cardiac arrest [24,25]. The reduction in metabolic activity after cardiac arrest is much stronger than can be induced by temperature changes in the range of 32–36 °C or by use of sedation in clinically relevant dosages. This suggests that interventions targeting temperature management, or blood pressure to improve outcome in these patients, have a low probability of effect. More likely, the regulation of CBF and metabolism is directly or indirectly under control of pathophysiological processes that determine neuronal survival. Loss of functional neural tissue after cardiac arrest is related to a large number of mechanisms, including excitotoxicity, disrupted calcium homeostasis, free radical formation, pathological protease cascades, and activation of cell-death signaling pathways [26]. Intervention studies aiming at manipulation of one or more of these pathways of injury may be more effective than enhancement of CBF during the post-cardiac arrest syndrome.

This study has a number of limitations. Although data were prospectively collected, it is a retrospective analysis of data in a relatively small sample from one single center. We found no signs of anaerobic metabolism, using a protocol aiming at relatively higher mean arterial pressures >80 mmHg. These relatively high perfusion pressures may provide sufficient CBF for aerobic metabolism, even in patients with a disturbed autoregulation. We found no evidence of anaerobic metabolism, using methods that measure global metabolism. We cannot exclude the possibility that regional ischemia might occur.

All patients were sedated and treated with hypothermia for 24–72 h. The effects of sedation and hypothermia may have affected our results. It is generally assumed that cooling reduces cortical activity, however, this is not a major factor in the temperature ranges that are used in these patients [27,28]. Propofol induced changes are well known. In the dosages that were used in the ICU, cortical activity remains continuous [29]. Even if discontinuity is induced, bursts are heterogeneous and suppressions are short [30]. This is a physiological response of a relatively healthy brain to sedation and contrasts with the abrupt discontinuation of all neuronal activity within 10–40 s after induction of hypoxia [31]. The patients in this study were treated with 24 or 72 h of hypothermia (and concomitant sedation). No significant differences were found in CBF or metabolism data were found between the 24 and 72 h treated groups. These data support the fact that the changes in CBF and metabolism is mainly related to the post-cardiac arrest state, rather than a hypothermia or sedation effect.

Derangements in pH and PaCO₂ probably influenced our results. Hypercapnia and/or acidosis can induce a reduction in cerebral metabolism. The pH-dependent activity of phosphofructokinase (the enzyme responsible for the phosphorylation of fructose 6-phosphate in glycolysis) provides mechanistic support for reductions in CMRO₂ with hypercapnia. Indeed, an accumulation of glucose 6-phosphate and fructose 6-phosphate is shown in rats exposed to acute hypercapnia [32]. Additionally, hypercapnia depresses cortical activity by acidosis-induced adenosine receptor modulation [33–35].

Conclusion

In this study, low cerebral perfusion after cardiac arrest was not associated with anaerobic metabolism. It is unknown if this hypoperfusion is the cause or consequence of a substantial decrease of neuronal functioning and metabolic needs. Metabolism increases in recovering patients – consistent with resumption of neuronal activity – whereas in patients with a poor outcome, low metabolism reflects irreversible neuronal damage.

The therapeutic and prognostic potential of these new parameters remain to be established.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.resuscitation.2017.08.218>.

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